Remarks

Currently Claims 1-11, 15 and 17-77 are pending.

Claim 26 is amended to recite that the CNS disorder is mediated by substance P. Support for this amendment may be found throughout Applicants' specification, including at original claim 16. No new matter is added.

New claims 67-77 are added. Claims 67-68 recite a compound within the scope of allowed claims 1, 10 and 11. Support for these claims can be found throughout Applicants specification including at original claims 1, 10 and 11 and Example 11a. New claims 69-72 recite the methods of treatment according to claims 26, 35, 39 and 42 using the compound now claimed in claim 67. Claim 73 recites a compound within the scope of allowed claims 1, 10 and 11. Support for these claims can be found throughout Applicants specification including at original claims 1, 10 and 11 and Example 14. New claims 74-77 recite the methods of treatment according to claims 26, 35, 39 and 42 using the compound now claimed in claim 73. No new matter is added.

Applicants acknowledge with appreciation the Examiner's indication that claims 1-11, 15, and 17-21 are allowed.

Applicants respectfully request clarification of the record with respect to certain points in the Office Action. Although claim 43 is pending, the restriction requirement fails to indicate in which of the Examiner's Groups this claim falls. Appropriate correction of the record is required. Claims 61-66 are indicated as falling with the Examiner's Group I, which was provisionally elected, with traverse, for examination. However, the Office Action indicates that claims 61-66 were withdrawn from consideration. Such action is not proper in light of the Examiner's grouping of claims and Applicants' provisional election of Group I. Consideration of claims 61-66 is requested.

Traversal of the Restriction Requirement

Claims 1-11, 15 and 17-66 are subject the a restriction requirement, the Office Action stating that the claims of Examiner's Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1. Applicants respectfully request re-consideration of the restriction requirement.

Unity of invention is satisfied where there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features that defines a contribution that the inventions make over the prior art. 37 CFR 1.475. Applicants respectfully submit that there is a technical relationship among the pending claims which involves the same or corresponding special technical feature, namely compounds of formula (I) and further that compounds of formula (I) define a contribution which the inventions make over the prior art. In this instance, a national stage application is deemed to have unity of invention where the claims are drawn to a product, a process specially adapted for the manufacture of the product and use of said product as they are here. All of the various uses and combination therapies specified in the claims are embodiments of the methods of treatment recited in claim 22. Accordingly, it is respectfully submitted that the instant claims share a special technical feature and represent the established categories of product, process for manufacture and use and withdrawal of the restriction requirement is respectfully requested.

For purposes of compliance with 37 CFR 1.499 and in the event that the restriction requirement is maintained, Applicants hereby affirm the election, with traverse, of the claims of the Examiner's Group I (i.e., claims 1-11, 15, 17-21, 26-30, 35, 36, 39, 42 and 61-66) for prosecution on the merits. To the extent that the restriction requirement is maintained, Applicants respectfully submit that new claims 67-77 should be examined with the Examiner's Group I. Applicants will await re-consideration of the restriction requirement before amending the claims to cancel non-elected subject matter.

Section 112, 1st Paragraph Rejection Overcome

Claims 26-30, 35, 36, 39 and 42 currently stand rejected under 35 U.S.C. §112, 1st Paragraph, the Office Action stating that the specification is not enabling for claims directed toward methods of treating CNS disorders, including the specific CNS disorders recited in claims 27-29, 35-37 and 42. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the disclosure is sufficient to enable one skilled in the art to make and use the claimed methods of treating CNS disorders mediated by substance P, including those specifically recited, with a compound of the invention.

The test for enablement is whether the disclosure contains sufficient information to enable one skilled in the art to make and use the invention that is claimed without undue experimentation. MPEP 2164.01. The Examiner bears the initial burden of establishing a reasonable basis for questioning the asserted enablement. MPEP 2164.04.

The Office Action does not dispute that the disclosure is sufficient to teach one skilled in the art how to: 1) make compounds of formula (I), 2) formulate them in dosage forms suitable for administration to a human or 3) administer the compounds to a human. Applicants understand the Examiner's rejection to be with regard to the teaching of how to use the compounds of the invention for the treatment of various CNS disorders mediated by substance P, and particularly, the Examiner's comments appear to question the efficacy of the compounds of the invention for the treatment of the specified disorders.

The Examiner is respectfully reminded that the scope of enablement depends not only on what is disclosed in the application but also on what is known to those of ordinary skill in the art. MPEP 2164.01(a), citing *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *see also, National Recovery Technologies v. Magnetic Separation Systems*, 49 USPQ2d 1671 (Fed. Cir. 1999). More specifically, where a statement of utility contains a connotation of how to use and/or the art recognized that standard modes of administration are known and contemplated, enablement is satisfied. MPEP 2164.01(c). It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. MPEP 2164.01(c). In this case, those skilled in the art already had the benefit of knowledge regarding methods of treating CNS disorders by administering other substance P (i.e., NK-1) antagonists, such as MK-869 (aprepitant). Based on the knowledge in the art at the time of filing regarding methods of treatment and dosages for compounds having similar biological activity, methods of treatment and dosing of substance P antagonist for the treatment of CNS disorders could be carried out by those skilled in the art without undue experimentation.

At the time of filing the instant application, substance P antagonists were known, as was the association between substance P and the treatment various CNS disorders

in humans, including major depressive disorders, anxiety, and panic disorders. U.S. Patent No. 5719147 granted 17 February 1998 to Merck is demonstrative of the knowledge in the art prior to Applicants' filing date. USPN '147 describes and claims substance P (NK-1 receptor) antagonists and methods of using such compounds for treatment of "disorders of the central nervous system". Col. 48, lines 18-23. The Examiner's attention is directed to USPN '147, col. 48, line 18 to col. 50, line 55 for the teaching of the CNS and other disorders which may be treated with the NK-1 antagonist. The Examiner is referred to the background of the patent for a summary of the knowledge in the art regarding the utility of NK-1 antagonists prior to Applicants' filing date. Pharmaceutical compositions for administration of an NK-1 antagonist are described at USPN '147, col. 50, line 56 through col. 52, line 13. Suitable dosages for the treatment of the disorders described appears at col. 52, line 60 through col. 53, line 23. *See also*, USPN 5872116, 6048859, 6096742, and 6235735.

As further evidence of the state of the art, the following articles describe methods of using substance P (NK-1) antagonists for the treatment of CNS disorders in humans, including those CNS disorders described and claimed in the instant application.

Kramer, et al., *Science* (1998) 281:1640-1645, stating:

> In a placebo-controlled trial in patients with moderate to severe major depression, robust antidepressant effects of the substance P antagonist MK-869 were consistent observed.... These findings suggest that substance P may play an important roll in psychiatric disorders.

Ballard, et al., *European Journal of Pharmacology* (2001) 412: 255-264, stating:

> The selective tachykinin NK1 receptor antagonist ... (MK-869) has been recently described as a novel therapeutic approach for anxiety/depression.... The data support a role for tachykinin NK1 receptor antagonists as novel anxiolyti/antidepressants.

Argyropoulos, et al., *Exp. Opin. Invest. Drugs* (2000) 9(8):1871-1875, stating:

> It has been suggested that, apart from pain, the NK1 antagonists may have a role to play in a number of conditions. This applies to both the periphery (inflammatory bowel disease, cystitis, psoriasis, asthma), and the CNS (emesis, migraine, schizophrenia, movement disorders, Alzheimer's, Parkinson's, multiple sclerosis, depression and anxiety). pg 1873.

Further examples of the state of the art in the use of substance P antagonists are readily available in the patent, medical and pharmacology literature. In view of the state of the art at the time of filing, it is unnecessary for Applicants' to repeat in the

specification the known correlation between substance P and the treatment of CNS disorders, known methods of treatment and dosing information.

NK-1 receptor binding affinity was, at the time of filing, a recognized tool for evaluating the ability of a compound to bind to the substance P (NK-1) receptor. *See*, USPN '147, col. 47, lines 36-60. Applicants believe that non-peptide compounds which bind to the substance P (NK-1) receptor are substance P (NK-1) antagonists. To Applicants knowledge, no non-peptide compounds which bind to the substance P (NK-1) receptor have been show to be substance P (NK-1) agonists. Applicants' specification, at page 12 teaches a functional experiment using fluorimetric imaging plate reader technology which may be employed by those skilled in the art to confirm substance P (NK-1) antagonism. In view of the teaching in the specification and the state of the art, the NK-1 receptor binding affinity and functional experiments do not require undue experimentation. The foregoing evidence demonstrates the correlation between substance P (NK-1) antagonism and the treatment of CNS disorders. Thus, Applicants' have demonstrated that it was within the skill of those in the art at the time of filing to treat CNS disorders by administering a substance P (NK-1) antagonist compound according to the invention.

The instant application discloses appropriate dosages of the compounds of the invention at page 18, lines 28-32. Applicants' disclosure, together with the knowledge in the art at the time of filing, as described above in connection with USPN '147, is clearly sufficient to teach one skilled in the art appropriate dosages for the treatment of the CNS disorders described and claimed in the instant application.

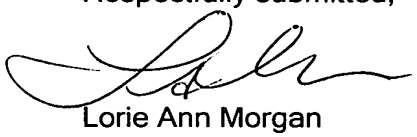
The Office Action states that Applicant gives no actual experimental data using these methods to treat a disease state, implying the experimental results in humans are required to satisfy the enablement requirement. Applicants respectfully submit that this is not the proper standard for enablement. There is no requirement that Applicants provide proof of efficacy in humans to meet the enablement requirement. It is sufficient for applicants to rely upon the knowledge of those in the art and evidence of pharmacological or other biological activity of a compound which is reasonably correlated, such as through scientific literature, to the asserted use. See MPEP 2107.03. Further, MPEP 2107.03 IV, reminds Examiners that they "should not

impose on applicants the unnecessary burden of providing evidence from human clinical trials."

Applicants have shown that that the compounds of the invention bind to the NK-1 receptor. The knowledge in the art at the time of filing included the knowledge that substance P (NK-1) antagonists are useful for the treatment of CNS disorders in humans, including those specifically recited in Applicant's specification and claims. Accordingly, the requirements of section 112 are satisfied and withdrawal of this rejection is respectfully requested.

Applicants respectfully submit that the instant application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact the undersigned at (919) 483-8222, to discuss this case, if desired.

Respectfully submitted,



Lorie Ann Morgan
Attorney for Applicants
Registration No. 38,181

Date: 9 February, 2006

GlaxoSmithKline Inc.
Five Moore Drive, PO Box 13398
Research Triangle Park
North Carolina 27709
(919) 483-8222
fax: (919) 483-7988
email: Lorie.A.Morgan@gsk.com